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## Activated endothelin system in polyglobulia

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**Abstract:** The role of the endothelin system, the functional counterpart of NO, in the pathophysiology of polyglobulia remains still elusive. Therefore a novel erythropoietin overexpressing mouse was generated, with hematocrit levels of about 80%. Hence, we analyzed vascular contractions to ET-1 and big endothelin-1 (big ET-1), endothelin-1 (ET-1) promoter activity, ET-1 immunochemistry, endothelin-1 (ET-1)-protein tissue levels, ETA/B-receptor mRNA expression in this novel transgenic model of severe polyglobulia. For analysis of ET-1 promoter activity, EPO transgenic mice were mated with homozygous transgenic mice expressing the lacZ gene under control of the human ET-1 promoter and immunohistochemistry for gal blue was performed in lacZ transgenic animals. Notwithstanding markedly increased eNOS expression, NO-mediated endothelium-dependent relaxation and circulating and vascular tissue NO levels indicating enhanced bioavailability of NO, ET-1 tissue levels were also augmented in heart, kidney, liver and aorta ( $2.2 \pm 0.3$  vs.  $0.5 \pm 0.1$  pg/mg tissue;  $P < 0.01$ ) of transgenic polyglobulic animals. Accordingly, immunohistochemistry demonstrated enhanced expression of ET-1 protein in the vascular wall of polyglobulic animals as compared to controls ( $p < 0.05$ ), while increase of ET-1 promoter activity was confined to the perivascular tissue ( $P < 0.05$ ). NOS inhibition with L-NAME unmasked increased vascular reactivity to ET-1 and bigET-1 and aortic ETA/B receptor mRNA gene expression was enhanced ( $p < 0.05$  vs. controls). Administration of the NOS inhibitor L-NAME led to acute vasoconstriction of peripheral resistance vessels, hypertension and death of transgenic mice within 2 days, while wildtypes did not show increased mortality. Treatment with the ETA antagonist darusentan doubled survival time of transgenic polyglobulic mice after NO synthase inhibition ( $p < 0.01$  vs placebo). In conclusion, in this study we provide first evidence that the tissue endothelin system is activated by polyglobulia. Together with a stimulated NO system it contributes to cardiovascular regulation in pathophysiological conditions associated with increased hematocrit

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## P-274

**ACTIVATED ENDOTHELIN SYSTEM IN POLYGLOBULIA**

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The role of the endothelin system, the functional counterpart of NO, in the pathophysiology of polyglobulia remains still elusive. Therefore a novel erythropoietin overexpressing mouse was generated, with hematocrit levels of about 80%.

Hence, we analyzed vascular contractions to ET-1 and big endothelin-1 (big ET-1), endothelin-1 (ET-1) promoter activity, ET-1 immunohistochemistry, endothelin-1 (ET-1)-protein tissue levels, ETA/B-receptor mRNA expression in this novel transgenic model of severe polyglobulia. For analysis of ET-1 promoter activity, EPO transgenic mice were mated with homozygous transgenic mice expressing the lacZ gene under control of the human ET-1 promoter and immunohistochemistry for gal blue was performed in lacZ transgenic animals.

Notwithstanding markedly increased eNOS expression, NO-mediated endothelium-dependent relaxation and circulating and vascular tissue NO levels indicating enhanced bioavailability of NO, ET-1 tissue levels were also augmented in heart, kidney, liver and aorta ( $2.2 \pm 0.3$  vs.  $0.5 \pm 0.1$  pg/mg tissue;  $P < 0.01$ ) of transgenic polyglobulic animals. Accordingly, immunohistochemistry demonstrated enhanced expression of ET-1 protein in the vascular wall of polyglobulic animals as compared to controls ( $p < 0.05$ ), while increase of ET-1 promoter activity was confined to the perivascular tissue ( $P < 0.05$ ). NOS inhibition with L-NAME unmasked increased vascular reactivity to ET-1 and bigET-1 and aortic ETA/B receptor mRNA gene expression was enhanced ( $p < 0.05$  vs. controls). Administration of the NOS inhibitor L-NAME led to acute vasoconstriction of peripheral resistance vessels, hypertension and death of transgenic mice within 2 days, while wildtypes did not show increased mortality. Treatment with the ETA antagonist darusentan doubled survival time of transgenic polyglobulic mice after NO synthase inhibition ( $p < 0.01$  vs placebo).

In conclusion, in this study we provide first evidence that the tissue endothelin system is activated by polyglobulia. Together with a stimulated NO system it contributes to cardiovascular regulation in pathophysiological conditions associated with increased hematocrit.

Key Words: Polyglobulia, Endothelin, Nitric Oxide

## P-275

**EXPERIMENTAL HEART FAILURE DUE TO AORTOCAVAL SHUNT: ROLE OF KININS AND ANP**

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Angiotensin II (AII) has been implicated as a pathogenetic factor in hypertension (HT) and therefore blockade of the AT1 angiotensin receptor has been considered a therapeutic approach to treat hypertension. The AT1 receptor is responsible for the majority of the known effects of AII; however, the role of AT2 receptor is less well defined. We hypothesized that blockade of AT1 receptors increases AII levels, which in turn activates the AT2 receptor and through a kinin pathway induces cardioprotection. In addition, we investigate whether or not AII modulates the release of ANP in rats with aortocaval shunt.

Fifty male Wistar rats ( $150 \pm 30$ g) were used. To induce heart failure, we relied on the aortocaval shunt, an established model of moderate high-output heart failure. Cardiac mass and plasma ANP and cardiac kininogenase activity were estimated.

Treatment with AT1 receptor antagonist Telmisartan significantly ( $p < 0.01$ ) increased kininogenase activity (from  $220 \pm 14$  pg/mg to  $1580 \pm 42$ ) and plasma levels of ANP (from  $48 \pm 5$  pg/ml to  $322 \pm 16$ ). Treatment with Telmisartan significantly ( $p < 0.01$ ) prevented cardiac mass increase and this effect was blunted by the kinin B2 receptor antagonist, icatibant and by the AT2 receptor antagonist PD123319.

Our results suggest that the AII-mediated stimulation of the AT2 receptor alone and/or through the release of kinins may be an important component of the cardioprotective effect of Telmisartan, perhaps acting via release of nitric oxide (NO) or by hyperpolarization caused by activation of potassium channels.

Key Words: Kinins, Angiotensin, Angiotensin Receptor Blockers

## P-276

**AUTOMATED VERSUS OPERATOR DIRECTED DIAMETER MEASUREMENTS FOR ENDOTHELIAL FUNCTION IN HYPERTENSIVE PATIENTS**

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Endothelial function (EF) measured by either coronary or peripheral arterial evaluation is an important prognostic marker for future cardiovascular events. However, these traditional arterial methods are invasive and carry a risk of injury to subjects. Flow-mediated brachial artery dilation (FMD) has emerged as a nitric oxide dependent method to measure EF in hypertensive subjects. Despite its relative safety, one major limitation of FMD is the limited quality of ultrasound images with poor delineation of vessel walls and M-lines. Traditionally, operator directed manual measurements of FMD are made on these ultrasound images but are very subjective and tedious. We postulated that automatic edge detection image analysis is superior to operator directed measurements of arterial diameter. We therefore examined the intra-observer repeatability of manual vessel diameter measurements versus automated edge detection based measurements in hypertensive subjects. Twenty ultrasound images of brachial arteries captured during FMD testing were selected to ensure variation of image quality and baseline vessel diameter and compared manual measurements and edge detection methods (Image Pro plus v4, Media Cybernetics, Silver Spring, MD). A single expert operator performed all measurements by selecting the area of interest and doing 5 manual measurements and 1 edge detection measurement on two occasions. We compared the 2 methods using Bland-Altman limits of agreement. The 20 images ranged in diameter from 3.14 mm to 5.67 mm. The two types of measurements had a significant correlation ( $R = 0.94$ ,  $P < .0001$ ), while the differences of the measurements had no correlation ( $R = .082$ ,  $P = .92$ ). The automated method had significantly narrower limits of agreement than the manual method. There was no linear relationship of the differences to the absolute vessel diameter. Automated edge detection is superior to operator directed brachial artery diameter measurements. This superiority of automated edge tracing over manual measurements will likely allow the detection of smaller changes in FMD in research studies.

| METHOD OF MEASUREMENT | Mean difference | $\pm 2$ standard deviation |
|-----------------------|-----------------|----------------------------|
| MANUAL                | -0.039          | -0.54 to +0.46             |
| AUTOMATIC             | +0.009          | -0.19 to +0.21             |

Key Words: Hypertension, Nitric Oxide, Endothelial Function